



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,793	04/09/2004	Luc J. Farmer	VPI/03-170 US	9337

27916 7590 01/18/2006

VERTEX PHARMACEUTICALS INC.
130 WAVERLY STREET
CAMBRIDGE, MA 02139-4242

EXAMINER

KOSACK, JOSEPH R

ART UNIT	PAPER NUMBER
----------	--------------

1626

DATE MAILED: 01/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/821,793	Applicant(s) FARMER ET AL.	
	Examiner Joseph Kosack	Art Unit 1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 December 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-53 is/are pending in the application.
- 4a) Of the above claim(s) 8-14, 30-34, 39 and 46-53 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7, 15-29, 35-38, and 40-45 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>3/02/2005</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-53 are pending in the instant application.

Election/Restrictions

Applicant's election without traverse of Group I, Claims 1-45 along with an election of species of Compound 69 on page 104 of the specification in the reply filed on December 6, 2005 is acknowledged.

As previously stated in the restriction requirement, in accordance with MPEP 821.04 and *In re Ochiai*, 71 F.3d 1565, 37 USPQ 1127 (Fed. Cir. 1995), rejoinder of product claims and method of use claims commensurate in scope with the allowed product claims will occur following a finding that the product claims are allowable. Until such time, a restriction between product claims and process is deemed proper.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

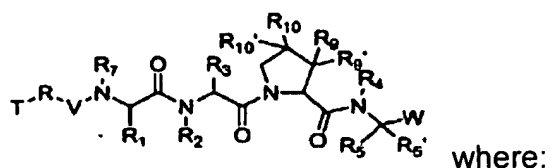
Status of the Claims

Claims 1-53 are pending in the instant application. Claims 1-7 (in part), Claims 8-14, Claims 15-29 (in part), Claims 30-34, Claims 35-38 (in part), Claim 39, Claims 40-45 (in part), and Claims 46-53 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. The withdrawn subject matter is patentably distinct from the elected subject matter as it differs in the

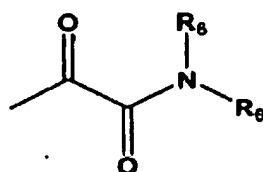
Art Unit: 1626

structure and element and would require separate search considerations. In addition, a reference, which anticipates one group, would not render obvious the other.

Pursuant to Applicant's election of a species, the scope of the invention will be limited to the following substitutions of the base structure



- T will be imidazole;
- R is a bond;
- V is -C(O)-;



- W is ;
- $R_9, R_{10}, R_{10'}$ are X-Y-Z where X & Y are bonds and Z is hydrogen;
- R_9 is X-Y-Z where X & Y are bonds and Z is C_{1-12} aliphatic, C_{3-10} cycloalkyl, or C_{3-10} cycloalkyl- C_{1-12} aliphatic, substituted as defined;
- all other substituents are as defined.

As a result of the election and the corresponding scope of the invention defined supra, the remaining subject matter of Claims 1-7, 15-29, 35-38, and 40-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected inventions. The withdrawn compounds contain varying functional groups such as pyrimidinyl, piperidinyl, imidazolyl, pyrrolidinyl, etc, which are chemically

Art Unit: 1626

recognized to differ in structure and function. This recognized chemical diversity of the functional groups can be seen by the various classification of these functional groups in the U.S. classification system, i.e. class 544 subclass 244(+) (diazines), class 546 subclass 184(+) (piperidines), 546 subclass 249(+) (pyridines), etc. Therefore the subject matter which are withdrawn from consideration as being non-elected subject matter differ materially in structure and composition and have been restricted properly a reference which anticipated but the elected subject matter would not even render obvious the withdrawn subject matter and the fields of search are not co-extensive.

Priority

The claim to priority of US Serial Number 60/513,765 filed on October 23, 2003 and US Serial Number 10/412,600 filed on April 11, 2003 has been acknowledged in the instant application.

Information Disclosure Statement

The Information Disclosure Statement filed on March 2, 2005 has been considered fully by the examiner.

Specification

The disclosure is objected to because of the following informalities: the specification defines a substituent J, which includes the group R', which can then be optionally substituted with another J group, leading to an indefinite number of compounds, found on page 14, line 28, through page 15, line 30.

Appropriate correction is required.

Claim Objections

Claims 1-7, 15-29, 35-38, and 40-45 are objected to for containing elected and non-elected subject matter. The elected subject matter have been identified supra.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-45 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the instant case, a pharmaceutical composition comprising compounds of Formula I is claimed.

In the art, the addition of therapeutic agents to a pharmaceutical composition consisting of a compound of interest and acceptable pharmaceutical carriers can affect the properties of the compound of interest. Properties affected can include binding constants, rates of diffusion, kinetics of reaction, receptor specificity, etc. The specification provides evidence that pharmaceutical compositions containing compounds of Formula I can contain one or more of immunomodulatory agents, antiviral agents, cytochrome P-450 inhibitors, etc, but not any evidence that these combinations have been attempted, or what their affect is on the properties of the

compound of Formula I. Therefore, only the pharmaceutical compositions that contain only the compound of Formula I and a pharmaceutically acceptable carrier meet the written description provision of 35 U.S.C. 112, first paragraph. It is suggested that Applicant include this limitation in their claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 15-29, 35-38, and 41-45 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims define a substituent J, which includes the group R', which can then be optionally substituted with another J group, leading to an indefinite number of compounds.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

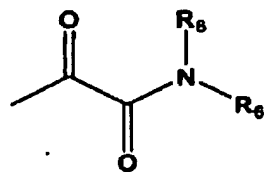
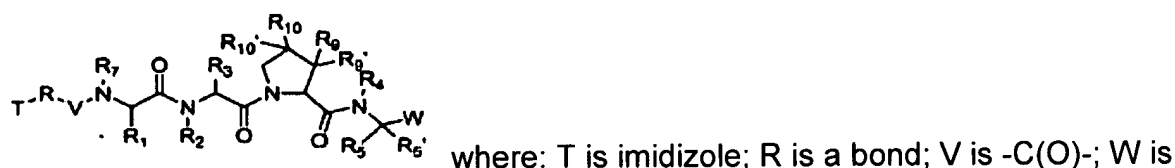
The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, 15-29, 35-38, and 40-45 rejected under 35 U.S.C. 103(a) as being unpatentable over Sasaki et al. (*J. Org. Chem.* 1997, 765-770) in view of Babine et al. (WO 02/18369).

The instant application cites a compound with a base structure:

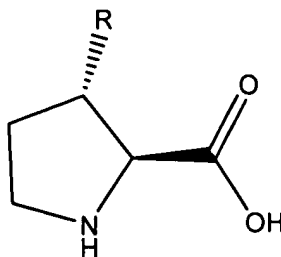


; R₉, R₁₀, R_{10'} are X-Y-Z where X & Y are bonds and Z is hydrogen;

R₉ is X-Y-Z where X & Y are bonds and Z is C₁₋₁₂ aliphatic, C₃₋₁₀ cycloalkyl, or C₃₋₁₀ cycloalkyl- C₁₋₁₂ aliphatic, substituted as defined; and all other substituents are as defined.

Determination of the scope and content of the prior art (MPEP §2141.01)

Sasaki et al. teach a synthesis of optically pure cis- and trans-3-alkyl substituted



proline derivatives having the formula:

See Scheme 3 on page

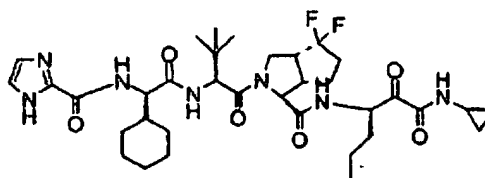
767.

Ascertainment of the difference between the prior art and the claims (MPEP

§2141.02)

Sasaki et al. do not teach the amidation of the proline nitrogen or the carboxylic acid with the substituents of the instant invention, or pharmaceutical compositions.

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)



Babine et al. teach the compound:

and its

synthesis in taking a proline derivative and amidating the proline nitrogen and the carboxylic acid to generate the compound above. See compound EN on page 65, and Scheme 11, page 120. Babine et al. also teaches a pharmaceutical composition comprising an effective amount of their compound, pharmaceutically acceptable carriers, and optionally another therapeutic agent. See page 264, line 14 through page 265, line 18 and page 298, line 30 through page 299, line 17.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make a 3-isopropyl substituted proline and use

Art Unit: 1626

in the synthesis scheme presented by Babine et al. with a reasonable expectation of success. The motivation to do so is provided by Babine et al. Babine et al. teach that inhibitors of HCV NS3-NS4A protease can be used as antiviral agents. See page 2, lines 18-34.

Thus, the claimed invention as a whole was *prima facie* obviousness over the combined teachings of the prior art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

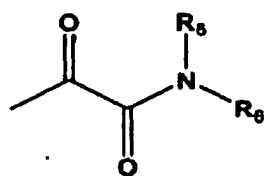
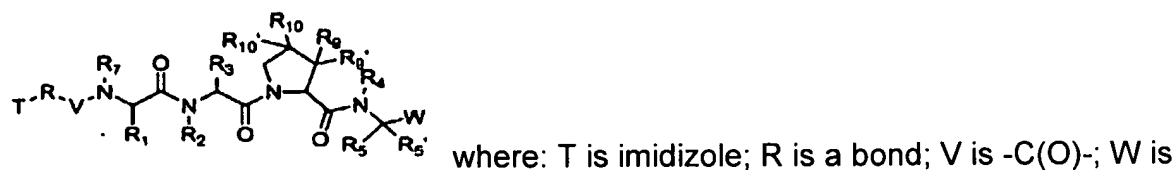
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 15-29, 35-38, and 40-45 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 4-16, 21-29, and 34 of copending Application No. 10/614,432, now published as US 20040077600 A1, in view of Patani et al. (*Chem. Rev.* 1996, 3147-3176).

Art Unit: 1626

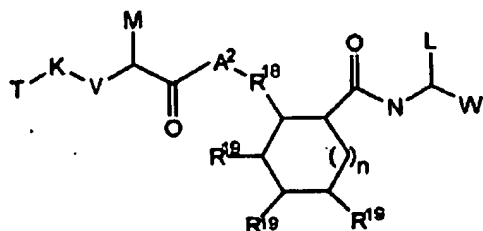
The instant application cites a compound with a base structure:



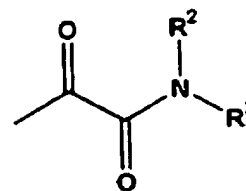
; R₉, R₁₀, R_{10'} are X-Y-Z where X & Y are bonds and Z is hydrogen;

R₉ is X-Y-Z where X & Y are bonds and Z is C₁₋₁₂ aliphatic, C₃₋₁₀ cycloalkyl, or C₃₋₁₀ cycloalkyl- C₁₋₁₂ aliphatic, substituted as defined; and all other substituents are as defined.

'432 teaches a compound with a base structure:



where n is 0; W is



; L is

alkyl, alkenyl, or alkynyl optionally substituted with halogen, sulfhydryl or hydroxyl; R¹⁸ is a bond, A² is -NR¹¹-CH(M)-C(O)-; V is NR¹¹, K is C(O), T is imidazole, R¹⁹ can be H or alkyl substituted with aryl, and all other substituents are as defined.

'432 does not teach a 5-membered ring with N bound to R¹⁸ instead of C to form an amide linkage instead of a ketone linkage.

Patani et al. teach the bioisosteric replacement of an CH group with N by Grimm's Hydride Displacement Law. See page 3148, column 2, lines 12-31.

Therefore it would have been obvious to one of ordinary skill in the art at the time of the claimed invention was made to take the compound of '432 and modify the the ring CH connected to R¹⁸ using the bioisosteric replacement of Patani et al. with a reasonable expectation of success. The motivation to make the claimed compound derives from the expectation that structurally similar starting materials are generally expected to have similar properties and have similar utilities. In re Gyurik, 596 F. 2d 1012, 201 USPQ 552 (CCPA 1979).

This is a provisional obviousness-type double patenting rejection.

Conclusion

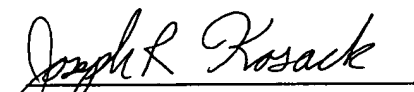
Claims 1-7, 15-29, 35-38, and 40-45 are rejected. Claims 1-7, 15-29, 35-38, and 40-45 are objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Kosack whose telephone number is (571)-272-5575. The examiner can normally be reached on M-F 7:30-4:00.

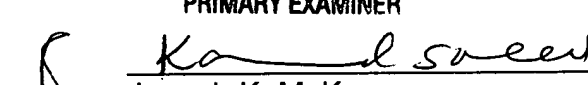
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1626

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Joseph Kosack
Patent Examiner
Art Unit 1626

KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER

for _____
Joseph K. McKane
Supervisory Patent Examiner
Art Unit 1626